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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/068,692	02/06/2002	Christopher J. O'Donnell	PC11080A	9227

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 01/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,692	O'DONNELL ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- Th MAILING DATE of this communication appears on the cov r sheet with the corr spondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-20 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-4 and 6-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

HOW TO MAKE: In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace substituted diazabicyclo compounds. The instant compounds of the formula wherein the n, m and o are other than m = 2, o = 1 and n = 1 are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-4, 6 and 7. For example where are the starting

materials for the preparation of compounds where the diazabicyclo ring is diazabicyclo[4.2.2]dodecane or diazabicyclo[3.3.2]dodecane, etc. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

HOW TO USE: Claims 9, 11, 13 and 15 are to "a method of treating schizophrenia or a disorder or condition which is responsive to the activity of $\alpha 7$ nicotinic receptor modulators. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. However, the specification provides no definitive evidence to correlate any one disorder selected from those disclosed in the specification with the instantly disclosed diazabicyclo derivatives.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed diazacyclo derivatives. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification does not have working examples on the use of the substituted diazabicylco[3.2.2]nonane, etc. The absence of working examples is one of the factors to be considered in deciding whether the practice of an invention would involve undue experimentation. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of schizophrenia, inflammatory bowel disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, etc.

2. Claims 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of treatment of chemical dependencies and addictions cannot be deemed enabled. The notion that a compound could be effective against chemical dependencies in general is contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for drug addiction generally. That is because drug addiction is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine re-uptake site. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system,

etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed.

3. Claims 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims are not adequately enabled solely based on its inhibitory effect on $\alpha 7$ nicotinic receptor provided in the specification. Recent studies on experimental and clinical pharmacology of $\alpha 7$ nicotinic receptors cited in Annual Reports in Medicinal Chemistry indicate that the following disorders may be associated with $\alpha 7$ nicotinic receptors: senile dementia of the Alzheimer's type, Parkinson's disease, Huntington's Chorea, tardive dyskinesia, hyperkinesia, mania, depression, attention deficit disorder, anxiety, dyslexia, schizophrenia, Tourette's syndrome and smoking cessation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein. The nicotinic effect with respect to Alzheimer's is hypothesized. Parkinson's Disease is presently of unknown etiology and recent studies have exhibited dosing problems as well as unusually high placebo effects. The pathophysiology of Tourette's Syndrome is unknown. The treatment of ulcerative colitis is currently limited to anti-inflammatories, immunosuppressants and antibiotics. Additionally, there are other pathological non-CNS conditions, such as

pouchitis and influenza virus-induced pneuomonitis, where nicotine efficacy has been reported, but remains to be confirmed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-15 are vague and indefinite in that it is not known what is meant by the definition of R^6, R^7 and R^8 where R^6, R^7 and R^8 is a (5-12 membered heteroaryl. There is no close parenthesis for this moiety.

b) Claims 1-15 are vague and indefinite in that it is not known what is meant by the definition of R^9, R^{10} and R^{11} where R^9, R^{10} and R^{11} is a (5-11 membered heterobicycloalkyl. There is no close parenthesis for this moiety.

c) Claim 6 is vague and indefinite in that it is not known what is meant by the definition of the substituents on Q where Q is straight chain or branched $(C_1\text{-}C_8)$alkyl, straight chain or branched $(C_2\text{-}C_8)$alkenyl, straight chain or branched $(C_2\text{-}C_8)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_4\text{-}C_8)$cycloalkenyl, 3-8 membered heterocycloalkyl, $(C_5\text{-}C_{11})$bicycloalkyl, $(C_7\text{-}C_{11})$bicycloalkenyl, 5-11 membered heterobicycloalkyl, 5-11 membered heterobicycloalkenyl, $(C_6\text{-}C_{11})$aryl, or 5-12 membered heteroaryl which is embraced by R^3 and thus results in double inclusion. See Ex parte White 127 USPQ 261.

d) Claims 10, 12 and 14 are substantial duplicates of claim 8, as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

e) Regarding claims 12-15, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

f) Claim 16 is vague and indefinite in that it is not known what is meant by carbothioic in line 27 on page 59.

g) Claim 16 is vague and indefinite in that it is not known what is meant by O-phenyl ester in line 27, page 59.

h) Claim 17 recites the limitation "bromo-phenyl" in the species of lines 3 and 18 on page 61. There is insufficient antecedent basis for this limitation in the claim.

i) Claim 17 recites the limitation "cyano-phenyl" in the species of line 4 on page 61. There is insufficient antecedent basis for this limitation in the claim.

j) Claim 17 recites the limitation "iodo-phenyl" in the species of lines 5, 12 and 21 on page 61. There is insufficient antecedent basis for this limitation in the claim.

k) Claim 17 recites the limitation "methoxy-phenyl" in the species of lines 6-8 on page 61. There is insufficient antecedent basis for this limitation in the claim.

l) Claim 17 recites the limitation "tert-butyl-phenyl" in the species of lines 9 and 19-20 on page 61. There is insufficient antecedent basis for this limitation in the claim.

m) Claim 17 recites the limitation "trifluoromethyl-phenyl" in the species of lines 10 and 15 on page 61. There is insufficient antecedent basis for this limitation in the claim.

n) Claim 17 recites the limitation "chloro-phenyl" in the species of lines 11 and 17 on page 61. There is insufficient antecedent basis for this limitation in the claim.

o) Claim 17 recites the limitation "cyano-biphenyl" in the species of lines 13 and 28 on page 61. There is insufficient antecedent basis for this limitation in the claim.

p) Claim 17 recites the limitation "bromo-biphenyl" in the species of line 14 on page 61. There is insufficient antecedent basis for this limitation in the claim.

q) Claim 17 recites the limitation "fluoro-phenyl" in the species of line 16 on page 61. There is insufficient antecedent basis for this limitation in the claim.

r) Claim 17 recites the limitation "phenoxy-phenyl" in the species of line 22 on page 61. There is insufficient antecedent basis for this limitation in the claim.

s) Claim 17 recites the limitation "methyl-biphenyl" in the species of lines 23 and 25 on page 61. There is insufficient antecedent basis for this limitation in the claim.

t) Claim 17 recites the limitation "chloro-biphenyl" in the species of lines 24, 26 and 27 on page 61. There is insufficient antecedent basis for this limitation in the claim.

u) Claim 17 recites the limitation "methoxy-biphenyl" in the species of line 29 on page 61. There is insufficient antecedent basis for this limitation in the claim.

v) Claim 17 recites the limitation "biphenyl" in the species of line 30 on page 61. There is insufficient antecedent basis for this limitation in the claim.

w) Claim 17 recites the limitation "bromo-dimethyl-phenyl" in the species of line 31 on page 61. There is insufficient antecedent basis for this limitation in the claim.

x) Claim 17 recites the limitation "bromo-methyl-phenyl" in the species of line 32 on page 61. There is insufficient antecedent basis for this limitation in the claim.

y) Claim 17 recites the limitation "bromo-chloro-phenyl" in the species of line 33 on page 61. There is insufficient antecedent basis for this limitation in the claim.

z) Claim 17 recites the limitation "dimethyl-phenyl" in the species of line 34 on page 61. There is insufficient antecedent basis for this limitation in the claim.

aa) Claim 18 recites the limitation "dimethyl-biphenyl" in the species of lines 1-5 on page 62. There is insufficient antecedent basis for this limitation in the claim.

ab) Claim 20 recites the limitation "bromo-phenyl" in the species of lines 9-10 on page 62. There is insufficient antecedent basis for this limitation in the claim.

ac) Claims 9, 11, 13 and 15 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of the $\alpha 7$ nicotinic receptor. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how

many patients need to be treated? If a successful treatment is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within

the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in analgesics, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3, 5, 6 and 8-15 are rejected under 35 U.S.C. 102(a) as being anticipated by GALLET et al., WO 00/58311. GALLET teaches the compounds, compositions and method of use of the compounds of formula I where the instant Q moiety is 4-nitro-phenyl. See example 6 on page 7 where R_3 is nitro.

6. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by HENRY et al., U.S. 3,954,766. HENRY teaches the compounds of formula I where m = 1; n = 1; o = 1; X is oxygen, Y is oxygen or NR^1 where R^1 is ethyl; and Q is ethyl. See claims 1-3.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 703-305-1880. The examiner can normally be reached on 8:30-5:00 Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner Art Unit 1624
January 20, 2004